Remarks

Priority

The outstanding Office Action indicates that a certified copy of the priority document had not been filed. Therefore, Applicants now provide a certified copy of French Application FR 01/07976 with this submission.

Information Disclosure Statement

The outstanding Office Action indicates that EP 0821960 and Golsteyn et al. were not considered. Applicants now provide English translations of EP 0821960 and Golsteyn et al. for consideration by the Examiner.

Specification

The specification is objected to for containing an embedded hyperlink and for improper disclosure of nucleotide sequences without a respective sequence identifier. The specification has been amended to delete the hyperlink and to add the sequence identifier. The Examiner further objects to the specification as it relates to Figure 8A, for improper disclosure of nucleotide sequences with out a respective sequence identifier; i.e., SEQ ID NOs as required under 37 CFR 1.821 through 1.825. Applicants, therefore, provide a computer readable form (CRF) copy of the sequence listing, a paper copy of the sequence listing, and a Statement that the content of the paper and computer readable copy are the same and includes no new matter as required under 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d). Applicants respectfully submit that the amendment obviate the grounds of the objection. Withdrawal of the objection to the specification is respectfully requested.

Claim Objections

Claims 43-47 are objected to for depending on a claim withdrawn from consideration. Claim 43 has been rewritten in independent form, and Claimss 44-47 have been amended to depend from

Claim 43. Withdrawal of the objection is respectfully requested.

Claim Rejections Under 35 U.S.C. §112

Claims 43-49 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement for reasons set forth on pages 4-6 of the Office Action. Claims 43-47 have been amended, and Claims 48 and 49 have been cancelled without prejudice or disclaimer. Accordingly, Applicants respectfully traverse the rejection.

Claim 43, as amended, is directed to a method of treating or preventing hepatocarcinomas comprising administering a therapeutically effective amount of a composition consisting essentially of an active agent which stabilizes an actin network of a cellular cytoskeleton and wherein said active agent is selected from the group consisting of: a zyxin protein or a polypeptide fragment thereof, a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, or an antisense nucleic acid thereof, a cell or set of cells overexpressing the zyxin gene or a functional fragment thereof, an inhibitor of cofilin, and a cyclic peptide.

As admitted by the Examiner, the specification "reasonably conveys the following agents which stabilize the actin network: zyxin protein, a nucleic acid molecule comprising or constituted of the zyxin gene, or an antisense nucleic acid thereof, a cell or a set of cells over expressing the zyxin gene or a protein coded for a fragment thereof and an inhibitor of cofilin such as Jasplakinolide or dolastatin 11." (The Office Action, page 5, lines 1-5). The specification also provides that the active agent can be a cyclic peptide (page 15, lines 6-7).

Claims 44-47 are directed to methods of treating or preventing mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies associated with chromosomal anomalies of region 7q34/q35 of a zyxin gene using the composition of claim 43. These claims are supported by the specification at least on page 2, paragraph [0011] and on page 13, paragraph [0053].

Accordingly, the amended claims 43-47 are fully supported by the specification. Claims 48 and 49 have been canceled. Withdrawal of the rejection to claims 43-47 under 35 U.S.C. §112, first paragraph, for lack of written description is respectfully requested.

Claims 43-49 further stand rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants respectfully traverse the rejection.

According to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), there are many factors to be considered when determining whether the specification provides an enabling disclosure or whether any necessary experimentation is "undue". These factors include, but are not limited to:

(A) the breadth of the claims;

(B) the nature of the invention;

(C) the state of the prior art;

(D) the level of one of ordinary skill;

(E) the level of predictability in the art;

(F) the amount of direction provided by the inventor;

(G) the existence of working examples; and

(H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, (Fed. Cir. 1988).

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The Examiner's analysis must consider all of the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id* at 1404, 1407.

With regard to the above described factors (factors A-H), the present claims 43-47 and 50 are directed to a method for treating or preventing hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma or malignant hemopathies associated with chromosomal anomalies of region 7q34/q35 of a zyxin gene by administering a therapeutically effective amount of a composition consisting essentially of an active agent which stabilizes an actin network of a cellular cytoskeleton and wherein said active agent is selected from the group consisting of: a zyxin protein or a polypeptide fragment thereof, a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, or an antisense nucleic acid thereof, a cell or set of cells overexpressing the zyxin gene or a functional fragment thereof, an inhibitor of cofilin, and a cyclic peptide.

The nature of the invention relates to the use of molecular biology and biological techniques for treatment of tumors.

In this field, a person of ordinary skill in the art typically has a Ph.D. or M.D., and some working experience in cell biology, protein chemistry, molecular biology and tumor immunology.

The present specification clearly discloses a method of treating or preventing hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma, malignant hemopathies associated with chromosomal anomalies of region 7q34/q35 of a zyxin gene as recited in Claims 43-47.

The specification further provides examples showing that expression of zyxin EWS-FLI cell lines reduces the tumorigenicity of the tumor cells in nude mice, and that inhibition of zyxin expression in non-tumorigenic NIH3T3 cells leads to the malignant transformation of these cells. These data established a direct link between the effect of malignant transformation and the level of expression of zyxin. In addition, the specification demonstrated that malignant tumor cells, such as

EWS-FLI cells, are deficient in cytoskeleton development, and provides examples showing that cofilin inhibitors, such as jasplakinolide and dolastatin 11, promote cytoskeleton development.

These examples clearly indicate that an agent which stabilizes an actin network of a cellular cytoskeleton, such as recited in Claim 43, would be effective in treating or preventing hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma, malignant hemopathies associated with chromosomal anomalies of region 7q34/q35 of a zyxin gene.

The Examiner alleges that the claim method reads upon a method of treating cancer by gene therapy and that the state of the art at the time of filing was such that one of ordinary skill could recognize the unpredictability of treating a disease by a method of gene therapy. Specifically, the Examiner cited Verma et al. (1997), Marshall (1995), Eck et al. (1996), Ross et al. (1996), Rubanyi (2001) and Juengst (2003) to support the notion that gene therapy is unpredictable. Applicants respectfully submit that most of the cited references were published several years before the time of the invention. Many successful gene therapy experiments had been conducted in both *in vitro* and *in vivo* models since the publication of these articles and the time of the present invention. In addition, Juengst (2003) was focused on gene therapy for one particular type of cancer. The predictability of gene therapy treatment for T cell-acute lymphoblastic leukemia does not necessarily apply to treatment claimed in the present invention.

The Examiner also cited Freshney (1983) for the notion that *in vitro* data may not correlate to *in vivo* results. Applicants respectfully submit that *in vitro* data have been widely used in the art to support *in vivo* experiments and good correlation between *in vitro* and *in vivo* results have been shown in many cases. Moreover, the present application provides examples demonstrating that the *in vitro* observation correlates with the *in vivo* results. For example, the *in vitro* observation that EWS-FLI cells lack actin filaments correlates with the *in vivo* tumorigenicity of these cells.

The Examiner further cited Gura (1997) to support the notion that treatment of cancer in general is, at the most, unpredictable. Applicants respectfully submit that predictability for each cancer treatment is different from the other. The present claims are based on solid scientific findings and are supported by *in vitro* and *in vivo* data.

In view of the foregoing, Applicants respectfully submit that based on the evidence regarding each of the above factors, the specification at the time the application was filed would have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. Withdrawal of the rejection to claims 43-47 under 35 U.S.C. §112, first paragraph, for lack of enablement, is respectfully requested.

Claim Rejections Under 35 U.S.C. §102

Claims 43-49 are rejected under 35 U.S.C. §102(b) as lacking novelty over Wallner et al. (WO 00/71135) and Posey et al. (*J. Bio.Chem.* 1999; 274: 4259-4265) for reasons set forth on pages 13-14 of the Office Action. Applicants respectfully traverse the rejection.

It is noted that a claim is anticipated only if each and every element as set forth in the claim is described in a single prior art reference.

Independent Claim 43, as amended, recites a method of treating or preventing hepatocarcinomas comprising administering a therapeutically effective amount of a composition consisting essentially of an active agent which stabilizes an actin network of a cellular cytoskeleton and wherein said active agent is selected from the group consisting of: a zyxin protein or a polypeptide fragment thereof, a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, or an antisense nucleic acid thereof, a cell or set of cells overexpressing the zyxin gene or a functional fragment thereof, an inhibitor of cofilin and a cyclic peptide.

In contrast, Wallner generally describes a method of treating a tumor by administering a therapeutically effective amount of **a boroproline derivative in combination with Jasplakinolide.** In other words, Wallner describes using two **active agents** in the composition: Jasplakinolide and boroproline. Wallner does not teach or suggest using "a composition consisting **essentially of an active agent** . . . is selected from the group consisting of: a zyxin protein or a polypeptide fragment thereof, a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, or an antisense nucleic acid thereof, a cell or set of cells overexpressing the zyxin gene or a functional fragment thereof, an inhibitor of cofilin and a cyclic peptide" as recited in claim 43. Accordingly, Applicants respectfully submit that Wallner does not anticipate claim 43 because it fails to disclose all claim limitations. Claims 44-47 and 50 depend from claim 43 and therefore, they are not anticipated by Wallner.

Posey was cited for its teaching that Jasplakinolide stabilizes the actin network of a cellular cytoskeleton. However, Posey does not disclose "a method of treating or preventing hepatocarcinomas comprising administering a therapeutically effective amount of a composition consisting essentially of an active agent which stabilizes an actin network of a cellular cytoskeleton and wherein said active agent is selected from the group consisting of: a zyxin protein or a polypeptide fragment thereof, a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, or an antisense nucleic acid thereof, a cell or set of cells overexpressing the zyxin gene or a functional fragment thereof, . . ." as recited in claim 43. Accordingly, Applicants respectfully submit that Posey does not anticipate claim 43 because it fails to disclose all claim limitations. Claims 44-47 and 50 depend from claim 43 and therefore, they are not anticipated by Posey.

Thus, the grounds for this rejection have been obviated and withdrawal of the 35 U.S.C. §102(b) rejection is respectfully requested.

Double Patenting

Claims 48 and 49 are objected to under 37 C.F.R. 1.75 as being a substantial duplicate of claims 43-47. Claims 48 and 49 are canceled. This ground of rejection is now moot.

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to contact attorneys listed below.

Respectfully submitted,

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